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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/645,706	08/24/2000	Keith V. Wood	341.005US1	3329

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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/645,706	WOOD ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,9,11,12,15,18,20,21,24-39,41-45,47,60,64,67,69-71,74,76-78 and 80-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *3/05*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,3-6,9,11,12,15,18,20,21,24-39,41-45,47,60,64,67,69-71,74,76-78 and 80-82.

Claims 2, 7, 8, 10, 13, 14, 16, 17, 19, 22, 23, 40, 46, 48-59, 61-63, 65, 66, 68, 72, 73, 75, and 79 have been canceled. Claims 1, 3-6, 9, 11, 12, 15, 18, 20, 21, 24-39, 41-45, 47, 60, 64, 67, 69-71, 74, 76-78, 80 and newly presented claims 81-82 are still at issue and are present for examination.

Applicants' arguments filed on 12/17/04, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim 64 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed 11/18/02.

Claims 1, 3-6, 9, 11, 12, 15, 18, 20, 21, 24-39, 41-45, 47, 60, 67, 69-71, 74, 76-78 and 80-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 (from which claims 3-6, 9, 11, 12, 15, 18, 20, 21, 24-39, 41-45, 60, 69, 70 and 81 depend), 47 (from which claims 71 and 82 depend), 67 (from which claims 69, 70 and 81 depend),

74 (from which claims 76, 77 and 81 depend), and 78 (from which claims 80 and 82 depend) are vague and indefinite in the recitation of "a reduced number of a combination of transcription factor binding sequences, intron splice sites, poly(A) addition sites and/or promoter sequences" as without knowing all the possible sequences which are considered to be transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences such a calculation is impossible as one could never obtain a count of the number of such sequence in any reference nucleic acid such that a skilled artisan could determine if the number in the first sequence is reduced relative to the number in the second sequence. While there are clearly art defined specific sequences within each of these categories, each of them is an open-ended group of sequences which includes many unknown members. Clearly while many transcription factors and their associated binding sequences are known in the art, new members are being added frequently such that the scope of the claims would change.

Applicants argue that that even if new members of any particular class of regulatory sites are recognized, regardless of how many members are in that class, the synthetic nucleic acid molecule of the invention is one having fewer sites which, in the absence of codon selection, would otherwise be introduced

and thus it is not indefinite. This is not persuasive because the addition of only new members is not the only issue with regard to identifying what sequences are within any one of these terms. Many such sites might be defined in either a narrow sense (i.e., only the most preferred sequences included) or in a much more broad sense including some variants of the most preferred sequences, such that different people may use different groups of sequences to define even the same set of sites. It is noted that pages 48-50 of the specification appear to define the specific sequences which applicant used for designing their synthetic nucleic acids (either giving specific sequences directly or by defining the specific version of a database searched with a specific program with specified parameters) which could be incorporated within the instant claims to overcome the instant rejection.

Claims 1 (from which claims 3-6, 9, 11, 12, 15, 18, 20, 21, 24-39, 41-45, 60, 69, 70 and 81 depend), 47 (from which claims 71 and 82 depend), 67 (from which claims 69, 70 and 81 depend), 74 (from which claims 76, 77 and 81 depend), and 78 (from which claims 80 and 82 depend) are vague and indefinite in the recitation of "are mammalian high usage codons selected to result in the second synthetic nucleic acid having a reduced number of … sequences relative to the wild type nucleic acid

sequence" as it is unclear whether any non-preferred codons may be present in the second synthetic nucleic acid and the language makes it unclear how the second synthetic nucleic acid differs from the wild type sequence. It is suggested that the claim be amended to recite "are mammalian high usage codons or codons selected to remove transcription factor binding sequences … sequences present in the wild type nucleic acid sequence".

Claims 1, 3-6, 9, 11, 12, 15, 20-21, 24-33, 35-39, 41-45, 47, 60, 67, 69, 70, 81, and 82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a variant of a parent DNA molecule encoding a reporter polypeptide identical to a reporter polypeptide encoded by said parent DNA, having more than 25% of the codons altered and having a reduced number of transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences than a mammalian codon optimized variant of the parent nucleic acid, (2) a variant of a parent DNA molecule encoding a luciferase having 90% identity to the polypeptide encoded by SEQ ID NO:2 and having more than 25% of the codons altered and having a reduced number of transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences than a mammalian codon optimized variant of SEQ ID NO:2 or (3) to any nucleic acid which will hybridize

to SEQ ID NO:9 under high stringency conditions and encode a polypeptide having luciferase activity, does not reasonably provide enablement for any variant DNA molecules encoding any reporter polypeptide having at least 90% identity to a wild type reporter polypeptide, having more than 25% of the codons altered and having a reduced number of transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences than a mammalian codon optimized version of the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO:9 under medium stringency conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The rejection is explained in the previous Office Action.

Applicants argue that the specification teaches several representative species of luciferase mutants with amino acid substitutions relative to a wild type sequence, which representative proteins have reporter activity and that numerous substitutions have been introduced into beetle luciferases without affecting the reporter property of the substitution variants. For instance, in U.S. Patent No. 6,602,677, five mutant luciferases are disclosed that have 12, 21, 32, 37, and 37 substitutions, respectively, relative to a parent luciferase.

Likewise, numerous substitutions have been introduced into other reporter proteins, such as GFP, chloramphenicol acetyl transferase and β-glucuronidase.

Applicants arguments are noted however the scope of enablement is not commensurate in scope with the claims. The vast majority of applicants claims are not limited to any particular reporter polypeptide. The extent of art guidance with regard to regions of each reporter polypeptide which can be successfully modified while retaining reporter activity varies widely. While some such as firefly or click beetle luciferases and GFP have been extensively modified and the art provides a substantial amount of guidance, for other reporter polypeptides, including many other luciferases (for example coelenterate luciferases), the amount of guidance provided by the art is highly limited at best. It should be noted that this rejection has been withdrawn for those claims in which the parent nucleic acid is limited to SEQ ID NO:2 (i.e., yellow-green click beetle luciferase YG #81-6G01 nucleic acid sequence).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the

art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-39, 41-45, 47, 60, 67-70, 74, 76, 77, 81 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sherf et al. (US Patent 5,670,356) in view of Zolotukhin et al. (US Patent 5,874,304), Donnelly et al. (WO 97/47358), Iannacone et al. and Pan et al. The rejection is explained in the previous Office Action.

Applicants argue with regard to the previous 103 rejection, that the combination of references does not disclose or suggest Applicant's invention as each reference discloses a different wav to modify the coding sequence of a gene to increase expression. This is not persuasive because each of these references is drawn to methods of increasing the expression of a gene in a desired host by altering the sequence of the nucleic acid but not the encoded protein in a variety of ways which will lead to increases in the production of desired protein. The

cited references show that the art was clearly aware that a combination of changes in codon preference and removal of sequences detrimental to transcription and/or translation in either the wild type gene or the codon optimized version can be used to accomplish this goal. While each of the cited references used a different combination of types of modifications, the art clearly teaches all of the claimed modifications encompassed in applicants claims (i.e., mammalian codon optimization, removal of transcription factor binding sequences, removal of splice sites, removal of potential promoters, and removal of polyadenylation sites) and clearly teaches combinations of them with one or more of the others.

Applicants further argue that none of the cited documents recognizes that codon replacement, may create additional transcription factor binding sites, and none of the cited documents removed transcription factor binding sites from a codon optimized gene. While it is true that none of the cited documents explicitly teach that codon replacements may create unwanted transcription factor binding sequences not present in the wild type sequence, Donnelly et al. and Pan et al. both show that the art recognized that codon modifications can **introduce** sequences which are unwanted within the synthetic gene, that additional codon modifications can decrease the introduction of

those sequences and Sherf et al. clearly teach that the presence of transcription factor binding sequences within a reporter gene is an unwanted feature as it may interfere with the desired genetic neutrality of the reporter gene (see column 8). Furthermore, it is obvious on its face that anytime a gene sequence is altered that one necessarily creates new sequences which were not previously present and that merely by random chance some of these newly created sequences may be detrimental. It is even further obvious on its face that the more changes one makes, the higher the chances that such a detrimental sequence will be introduced. (It is noted that the declaration of Dr. Wood submitted with the instant response clearly illustrates that this is true but appears to add little to applicants argument). Sherf et al. made only limited changes to codon selection and thus at least in his explicit teachings focused on the elimination of detrimental sequences present in the wild type sequence. However, the remaining art clearly would have motivated one of skill in the art to make more substantial changes in codon preference within the luciferase of Sherf et al. Furthermore the disclosures of Donnelly et al. and Pan et al. would have clearly led a skilled artisan to scan not only the wild type sequence for the unwanted transcription factor binding sites but also the codon optimized version thereof.

Applicants argue that if altering codon composition in an open reading frame to codons preferred in a heterologous host alone increases expression in the heterologous host, then there would be no motivation for the art worker to make any other changes, e.g., those which may reduce aberrant transcription. And that the cited art does not point to which changes in combination, i.e., a combination of transcription factor binding sites, and intron splice sites, poly(A) sites and/or promoter sequences would be useful in that regard. This is not persuasive because merely because one has made a useful improvement in something does not stop a skilled artisan from seeking additional improvements also. The art clearly teaches several distinct methods of increasing expression of a gene in a heterologous host which a skilled artisan would clearly be motivated to combine with the expectation that the combination would be superior to any of the methods alone. Furthermore, applicants argument that the cited art does not point to which combination of methods would be useful is not persuasive as applicants claims are not drawn to any combination in particular (note all applicants claims recite a combination of transcription factor binding sites, intron splice sites, poly(A) sites and/or promoter sequences such that any combination of one

or more of these is included) and the art clearly teaches several combinations of these.

Applicants finally argue that one of ordinary skill in the art in possession of the cited art would have no reasonable expectation that any particular set of changes would improve activity in a gene that is to be expressed in a highly evolutionarily distinct cell. This is not persuasive because the art clearly provide an expectation that codon optimization and the elimination of a variety of types of sequences which are detrimental to transcription and/or translation will improve the expression of a gene in a heterologous host. While it is acknowledged that one cannot be certain that the modifications will not have unexpected consequences, applicants are reminded that obviousness does not require an absolute certainty of success but only a reasonable expectation thereof.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS

of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (571) 272-0937. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Rebecca Prouty
Primary Examiner
Art Unit 1652